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Bronchiolitis Obliterans in Chronic Graft-versus-Host Disease: Analysis of Risk Factors and Treatment Outcomes

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ABSTRACT

Bronchiolitis obliterans (BrOb), a late complication of bone marrow transplantation (BMT), is associated with chronic graft-versus-host disease (GVHD) and is frequently fatal. To identify the risk factors associated with BrOb, the factors affecting survival, treatment outcomes, and causes of death of patients with BrOb, we retrospectively analyzed 2859 BMT recipients. No cases of BrOb occurred among 1070 autologous BMT recipients. Among 1789 allogeneic BMT recipients, we identified 47 patients with BrOb. In multivariate analysis, older recipients or donors and acute GVHD were significantly associated with the development of BrOb. Among patients with BrOb, 5-year survival from the time of transplantation was only 10%, versus 40% among allogeneic BMT recipients without BrOb. The clinical course of BrOb had a significant effect on survival: 79% survived 5 years from the time of BrOb diagnosis if BrOb improved versus 13% if there was no improvement after the first-line therapy. Predictors of response included older donors and recipients, a previous diagnosis of chronic GVHD, and diagnosis of BrOb 6 months after transplantation; each of these significantly increased the likelihood of a favorable response to treatment. BrOb had high mortality rate of 55%, and pulmonary failure was the leading cause of death. More effective BrOb therapy is needed, especially for patients with unfavorable presentation.

KEY WORDS

Obstructive lung disease • GVHD • Late complications • Allogeneic bone marrow transplantation

INTRODUCTION

Allogeneic bone marrow transplantation (BMT) has revolutionized the therapeutic approach toward acute and chronic leukemia, aplastic anemia, and rare immunodeficiency disorders. Half of all patients who undergo BMT achieve long-term disease-free survival, but a similar number develop significant complications. Pulmonary complications remain frequent cause of posttransplantation mortality [1-4]. With prolonged survival after BMT, there is an increased recognition of the relatively late posttransplantation syndrome of bronchiolitis obliterans (BrOb).

BrOb, an obstructive pulmonary disease of small airways after BMT, was first described by Roca et al. [5] in 1982 in a patient with chronic graft-versus-host disease (cGVHD). Since then, several studies have reported a 2% to 20% incidence of BrOb in BMT patients. Despite the variety of therapeutic protocols, the mortality of BrOb is very high, ranging from 21% to 100% [6-13]. With the exception of 3 described cases of BrOb after autologous BMT [14,15], the late-onset posttransplantation obstructive lung disease primarily affects allogeneic recipients. It has been associated with cGVHD, use of methotrexate for GVHD prophylaxis, and hypogammaglobulinemia [7-9].

The pathogenesis of BrOb in BMT recipients has not yet been well defined. It has been suggested that the changes leading to the cicatricial form of BrOb may evolve from interstitial pneumonia and BrOb-organizing pneumonia (BOOP) [16]. Donor lymphocytes targeting host epithelial cells are implicated by

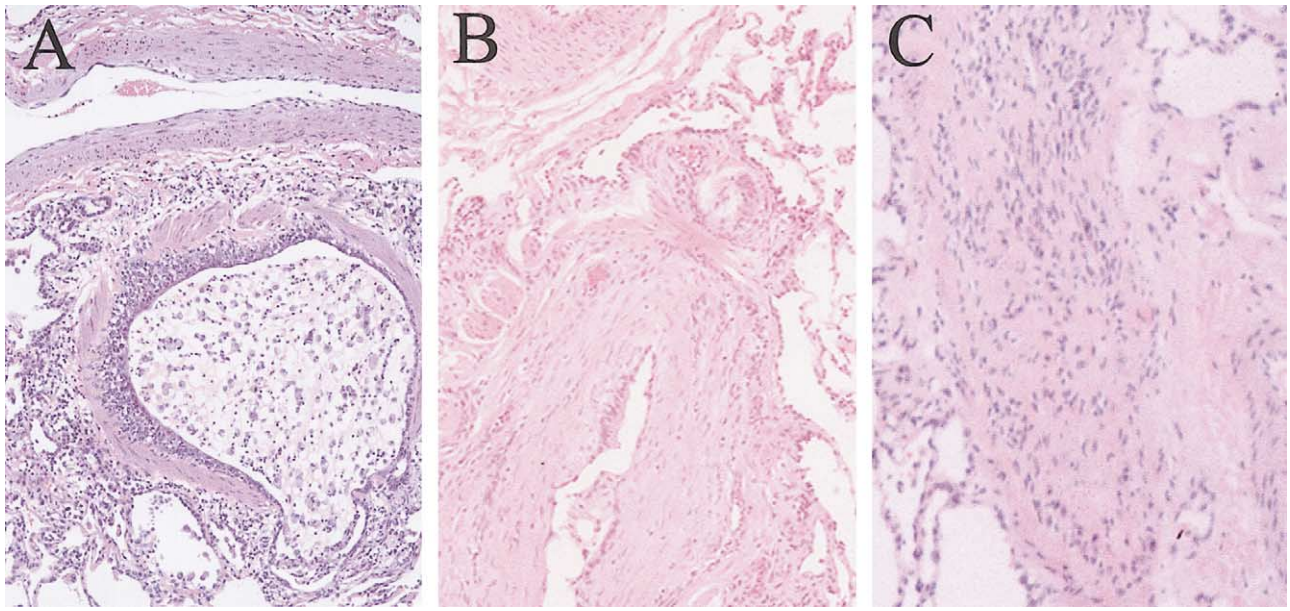

Figure 1. Lymphocytic bronchiolitis (A) and partial (B) and total (C) obliteration of bronchioles in BrOb.

the graft-versus-host reaction in an animal model [17]. The onset of BrOb is often insidious. It may start without initial respiratory symptoms, with normal-appearing or hyperinflated lungs on chest radiograms, and thus the disease is difficult to diagnose and treat at an early stage. Furthermore, the variable clinical course of BrOb [8] may suggest the existence of yet-unknown factors involved in its pathophysiology. Differences in reported outcomes may be due to the inclusion of BOOP in some series, a distinctly different disease entity with a usually favorable response to steroid therapy [18-21].

In this study, we retrospectively analyzed 2859 BMT recipients to determine risk factors for BrOb, factors affecting survival, treatment outcomes after different therapeutic regimens, and causes of death for patients diagnosed with BrOb.

METHODS

Study Population

We retrospectively analyzed 2859 patients who received BMT at the University of Minnesota between January 1, 1980, and January 31, 1999. The database was searched for patients with a diagnosis of BrOb, BOOP, pulmonary GVHD, or interstitial pneumonitis, and when patients were found, their database records were reviewed in detail. Patients with an identified infectious cause of pulmonary disease, confirmed diagnosis of BOOP, or interstitial pneumonitis without features of pulmonary GVHD were excluded from further review, leaving 68 cases with a possible diagnosis of BrOb. All medical records and available histopathologic materials were further reviewed to confirm this diagnosis. Twenty-one patients were excluded from further analysis because they did not have pathologic proof of disease and did not meet criteria for clinical diagnosis, and 47 patients with a confirmed diagnosis of BrOb were then evaluated. The diagnosis of BrOb was determined by either histopathologic (n = 39) or clinical (n = 8) evidence. These patients represent confirmed although possibly incomplete, case ascertainment.

Histopathologic criteria for BrOb were used in accordance with previously published morphologic standards [9] and included obliteration of the airway lumen of terminal bronchioles due to granulation tissue containing peribronchial, bronchial, and perivascular mononuclear infiltrates (Figure 1). Lymphocytic bronchiolitis—characterized by lymphocytic subendothelial, epithelial, and submucosal infiltration with frequent single-cell necrosis—was included in our study and categorized as a variant of lung GVHD. Other lung injuries identified in conjunction with GVHD [22], such as diffuse alveolar damage and interstitial pneumonitis, were included in study only if they were accompanied by changes typical of BrOb. Histopathologic diagnosis of BrOb was made in 39 patients: 34 by open lung biopsy, 4 by transbronchial lung biopsy, and 1 at autopsy.

Clinical diagnosis of BrOb was defined by moderate to severe obstructive ventilatory defects: forced expiratory volume in 1 second (FEV_1) <70% and FEV_1/forced vital capacity <80% of the predicted value [7,8] along with typical changes on high-resolution computed tomography. These included areas of decreased attenuation of lung parenchyma, expiratory air trapping, and subsegmental or segmental bronchial

dilatation [23,24]. A clinical diagnosis also required exclusion of infectious causes recognized on extensive microbiologic and virologic tests of alveolar lavage and biopsy specimens. Eight patients were diagnosed with BrOb on the basis of clinical evidence.

The diagnosis of cGVHD was made by using published criteria for clinical signs and symptoms and by histopathologic examination of skin [25], oral mucosa [26], esophageal, liver [27,28], and bronchial and open lung biopsy samples [29]. Pretransplantation and posttransplantation details of all patients included in the study were retrieved from the University of Minnesota Blood and Marrow Transplant Database, which contains prospectively collected extensive clinical data on all patients who have undergone transplantation at our center.

Statistical Analysis

To determine risk factors associated with the development of BrOb, the following characteristics were considered in univariate and multiple regression analyses: recipient and donor age, donor and recipient sex, sex mismatch, disease treated with transplants, related or unrelated donor, HLA match, type of preparative regimen, acute GVHD, source of stem cells, year of transplantation, GVHD prophylaxis, and cytomegalovirus (CMV) serostatus. We could not include cGVHD as a risk factor, because BrOb, considered to be a pulmonary manifestation of cGVHD, was an end point of this analysis. The cumulative incidence of BrOb was calculated by treating death from other causes as a competing risk. Univariate comparisons were performed by using the Mantel-Cox log-rank test statistic. To evaluate the independent effects of potential risk factors, forward stepwise regression was performed with factors retained in the model if $P < .1$ [30,31]. Nonbaseline factors, such as acute GVHD and cGVHD, were treated as time dependent.

Clinical improvement (response) was defined by a 10% improvement in FEV_1 and a sustained reduction in the symptoms of shortness of breath and cough reported to physicians. The following variables were considered as factors potentially modifying the frequency of response: age of donor and recipient, related or unrelated transplant, source of stem cells, prior acute GVHD, prior cGVHD, duration of prior cGVHD, time from transplantation, severity of lung damage assessed by pulmonary function test (PFT); and clinical versus pathologic diagnosis.

Survival was estimated by the Kaplan-Meier method [32]. The survival of patients diagnosed with BrOb was compared with the survival of BMT recipients who did not develop BrOb and with the survival of BMT recipients with GVHD, treating the development of BrOb as a time-dependent variable [33]. The influence on survival of patient demographics, severity of lung damage as assessed by PFT, clinical parameters of BrOb, regimens used to treat BrOb, levels of immunoglobulin, and course of BrOb after therapy was determined by the log-rank test. Cox regression was used to examine the independent effects of these variables on survival.

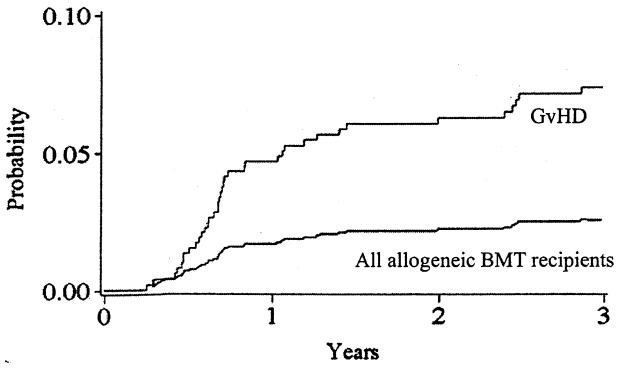

Figure 2. Incidence of bronchiolitis obliterans in recipients of allogeneic transplantation and in patients with GVHD.

RESULTS

Prevalence of BrOb after Allogeneic BMT at the University of Minnesota

Between 1980 and 1999, 2859 patients underwent BMT (median age, 24.7 years; range, 0.1-67.4 years; male, n = 1628; female, n = 1231). A total of 1789 patients were allogeneic recipients, and 1070 were autologous recipients. Forty-seven of 1789 allogeneic recipients, but none of the autologous recipients, developed BrOb. Twenty-nine BrOb patients were males, and 18 were females (median age, 26.9 years; range, 4-50.1 years). The median time from transplantation to the onset of BrOb was 465 days (range, 77-3212 days). Of 47 BrOb patients, 38 were already diagnosed with cGVHD before the onset of BrOb. The cumulative incidence of BrOb among allogeneic BMT patients was 2% at 1 year and 3% (95% confidence interval, 2%-4%) at 3 years after transplantation. Among those with cGVHD, the incidence of BrOb was 6% at 1 year and 7% (5%-9%) at 3 years after transplantation (Figure 2).

Risk Factors for BrOb

In the univariate analysis, BrOb was found to be more frequent in older patients and in recipients with older donors (Table 1). The 3-year incidence of BrOb was 0.4% for 0- to 9-year-old recipients, 5% for 10- to 19-year-old recipients, and 3% for recipients ≥20 years of age ($P < .01$). Similarly, the 3-year incidence was 0.4% if donors were 0 to 9 years old, 4% if 10 to 19 years old, and 3% if ≥20 years of age ($P < .01$).

Table 1. *Incidence of Bronchiolitis Obliterans after Bone Marrow Transplantation*

Variable	No. of Cases		3-y Incidence of BrOb (95% CI)	*P* Value
	Total	With BrOb		
All allogeneic BMT recipients	1789	44	3% (2%-4%)	
Patients with chronic GVHD	536	38	7% (5%-9%)	
Recipient's age at the time of BMT (y)				
0-9	571	2	0.4% (0%-1%)	
10-19	331	16	5% (3%-7%)	<.01
20-29+	887	26	3% (2%-4%)	
Donor's age at the time of BMT (y)				
0-9	269	1	0.4% (0%-1%)	
10-19	200	7	4% (2%-6%)	.01
>20	1233	33	3% (2%-4%)	
Donor and recipient sex match				
Male/male	533	11	2% (1%-3%)	
Male/female	474	16	3% (1%-5%)	NS
Female/male	371	9	2% (0%-4%)	
Female/female	353	8	2% (0%-4%)	
Cord blood	58	0	0%	
Disease treated with BMT				
Nonmalignant diseases	437	6	1% (0%-2%)	
Acute leukemia	703	14	2% (1%-3%)	
CML	452	21	5% (3%-7%)	.02
MDS	97	1	1% (0%-3%)	
Other malignancies	100	2	2% (0%-5%)	
Donor and recipient match				
Related donor, HLA matched	1069	33	3% (2%-4%)	
Related donor, HLA mismatched	93	1	1% (0%-2%)	
Unrelated donor, HLA matched	278	6	2% (0%-4%)	NS
Unrelated donor, HLA mismatched	290	3	1% (0%-2%)	
Cord blood	58	0	0%	
Episode of acute GVHD				
Yes	1045	37	4% (3%-5%)	<.01
No	744	7	1% (0%-2%)	
Source of stem cells				
Bone marrow	1670	41	3% (2%-4%)	
PBSC	61	3	8% (0%-18%)	.13
Cord blood	58	0	0%	
Year of transplantation				
1980-1984	293	7	2% (0%-4%)	
1985-1989	415	11	3% (1%-5%)	
1990-1994	577	13	2% (1%-3%)	NS
1995-1998	504	13	3% (1%-5%)	
Conditioning regimen				
TBI	1489	36	3% (2%-4%)	
Bu/Cy	123	3	2% (1%-3%)	NS
Other	177	5	3% (2%-4%)	
GVHD prophylaxis				
Methotrexate	1262	34	3% (2%-4%)	
Cyclosporine	73	1	2% (0%-5%)	
T-cell depletion	369	5	1% (0%-2%)	.11
Cord blood plus cyclosporine	39	0	0%	
Other	46	4	8% (0%-16%)	
CMV serostatus				
Recipients and donors both negative	565	17	3% (2%-4%)	
Recipient negative, donor positive	226	5	2% (0%-4%)	NS
Recipient positive	954	22	2% (1%-3%)	

CI indicates confidence interval; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; PBCS, peripheral blood stem cells; TBI, total body irradiation; Bu/Cy, busulfan plus cyclophosphamide; NS, not significant.

Transplantations performed for nonmalignant diseases (eg, aplastic or Fanconi anemia) resulted in a 1% BrOb 3-year incidence, 2% for acute leukemia, 5% for chronic myelogenous leukemia, 1% for myelodysplastic syndrome, and 2% if performed for other malignancies (eg, non-Hodgkin lymphoma; $P = .02$). Patients with acute GVHD had 4% 3-year incidence of BrOb versus those with no history of acute GVHD

Table 2. *Multiple Regression Analysis of Risk Factors for BrOb*

Variable	Relative Risk (95% CI)	*P* Value
Donor or recipient age (y)		
<10*	**1.0**	
10-20	**15.3 (3.5-66.2)**	**<.01**
≥20	**9.9 (2.4-42.0)**	**<.01**
Acute GVHD		
No*	**1.0**	
Yes	**2.6 (1.3-4.9)**	**<.01**

*Reference pair.

(1% incidence; $P < .01$). During the study (1980-1998), there was no difference in the incidence of BrOb between time periods (Table 1).

Cox regression analysis identified older donor and recipient age and prior acute GVHD as statistically significant independent predictors of BrOb (Table 2). Type of disease treated with BMT, type of donor, source of stem cells, and CMV serostatus were not associated with the development of BrOb.

Treatment of BrOb

In 23 of 47 patients, BrOb improved after treatment; in 8 patients, it remained stable for at least 3 months but later worsened; and in 16 cases, BrOb progressively worsened despite treatment (Table 3).

Six patients were treated with antithymocyte globulin (15 mg/kg intravenously for 5 days), bolus methylprednisolone (250 mg/m^2 intravenously twice a day for 5 days and then weekly for 8 weeks at 15 mg/kg), daily prednisone (60 mg/m^2), and cyclosporine (1.5 mg/kg intravenously every 12 hours). Two of these patients had improvement of BrOb, 1 had stable disease (for 3 months) and then a later progressive course despite the addition of thalidomide (initially 50 mg 4 times a day with a further increase up to 800 mg daily), and 3 had progressive disease.

Twenty-seven patients were treated with weekly bolus methylprednisolone (for 8 weeks at 15 mg/kg), prednisone every other day (0.5 mg/kg orally), and either cyclosporine (6.25 mg/kg every 12 hours orally) or azathioprine (0.5 mg/kg/d). Fifteen patients (6 treated with azathioprine and 9 with cyclosporine) had improvement in BrOb; 3 had stable and then progressive disease, and 9 had progressive disease after initial therapy. Three patients were also given thalidomide; 2 patients responded, 1 with initially progressive disease, and one continued to have progressive disease despite the addition of thalidomide.

In the group of 14 patients treated with prednisone (1 mg/kg orally) alone or with cyclosporine or azathioprine, 6 patients had BrOb improvement, 4 had stable and then later progressive disease, and 4 had progressive disease. One patient in this group also received thalidomide but continued to have progressive disease.

Factors Predicting Response in BrOb

The extent of pulmonary damage reflected by PFT was not predictive of response ($P = .37$). Whereas 55% of BrOb patients who had cGVHD responded to initial therapy, no patient without prior cGVHD responded to initial therapy ($P = .02$). Older patients or those with older donors had responsive disease more frequently ($P < .01$); (Table 4). In addition, onset of BrOb >6 months after transplantation was associated with a higher likelihood of response to therapy (58% versus 17%; $P = .01$; Figure 3). Eight patients were diagnosed with BrOb by using clinical criteria. They had a higher likelihood of response than patients diagnosed by biopsy ($P = .02$). Patients with BrOb who responded to first-line therapy had a superior 5-year survival of 79% versus 13% for those whose initial therapy failed.

Survival

BrOb was a major factor associated with poor survival after transplantation. At 5 years, only 10% of BrOb patients survived, versus 40% of transplant recipients without BrOb ($P < .01$). Among patients diagnosed with cGVHD, but without BrOb, the chance of 5-year survival was 54%, versus only 29% among those with both cGVHD and BrOb ($P < .01$; Table 5). Patients with low immunoglobulin G levels at the time of BrOb diagnosis had a 35% probability of survival at 5 years, versus 64% if they had a normal immunoglobulin G level; however, this difference was not statistically significant. The type of BrOb treatment and the course of BrOb were examined for their effect on survival in patients with BrOb, but only the response to initial therapy was critical. The likelihood of 5-year survival was 79% if BrOb improved after first-line therapy, whereas it was only 13% if BrOb either was stable or worsened after initial therapy ($P <$

Table 3. *Outcome of Patients with BrOb: Response to First-Line Therapy Yields Better Survival*

Response to Therapy	No. of Patients	No. of Patients Who Died of BrOb	No. of Patients Who Died of Infection
Response	**23**	**1**	**2**
Stable and then progressive BrOb	**8**	**1**	**6**
Progressive BrOb	**16**	**10**	**3**

Table 4. *Factors Affecting the Clinical Course of BrOb*

Factors Affecting the Clinical Course of BrOb	No. of Patients	No. of Responders (%)	*P* Value
Chronic GVHD			
No	6	0	.02
Yes	41	23 (55)	
Time from transplantation to BrOb (mo)			
<6	12	2 (17)	.01
≥6	35	21 (58)	
Type of diagnosis			
Clinical	8	7 (88)	.02
Pathologic	39	16 (40)	
Influence of Age on Clinical Course	**No. of Patients**	**Median Recipient Age (y)**	***P* Value**
Clinical outcome			
Improved	23	33.7 (9.8-49.4)	
Not improved	24	16.3 (4-50.1)	<.01
		Median donor age (y)	
Improved	23	34.1 (21.8-50.8)	
Not improved	24	23.2 (8.3-49.5)	<.01

.01; Figure 4). The extent of pulmonary damage reflected by PFT was not predictive of survival (P = .28); however, patients with improving lung function as measured by PFT had a significantly better likelihood of 5-year survival (P = .05; Figure 5). We tested factors influencing survival among allogeneic patients with cGVHD by Cox regression analysis. The diagnosis of BrOb (relative risk [RR], 2.0; $P < .01$), older donor age (RR, 1.1 per decade; P = .03), GVHD prophylaxis other than T-cell depletion (RR, 2.1; $P <$ .01), and prior grade II to IV acute GVHD (RR, 1.9; $P < .01$) were each found to be independently significant factors associated with shorter survival.

Causes of Death in Patients with BrOb

Of 47 patients with BrOb, 26 died during the study. Twelve patients died of progressive lung disease associated with continuing cGVHD and pulmonary failure. One patient died of pulmonary hemorrhage during therapy for progressive multiorgan cGVHD. Ten patients died of pulmonary infection: 5 fungal (4 *Aspergillus* species and 1 *Candida glabrata*), 4 bacterial (*Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and other Gram-positive cocci), and 1 viral (influenza A). In 9 of the 10 patients who died of respiratory infection, 9 had progressive BrOb and were receiving continuing immunosuppression. Three patients died of nonpulmonary causes: Epstein-Barr virus—related lymphoproliferative disease, progressive adrenoleukodystrophy, and *E. coli* meningitis.

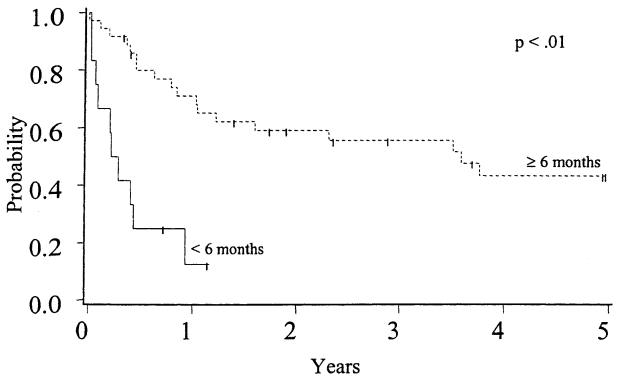

Figure 3. Survival after diagnosis of BrOb: late onset yields better survival.

DISCUSSION

BrOb, a pathology of terminal bronchioles, can be seen as an outcome of number of pathologic processes; rheumatoid arthritis, toxicity of chrysotherapy, influenza virus, and adenovirus type 2 pulmonary infections in children, as well as lung and bone marrow transplantation. In the last group, this pathologic process can be a form of cGVHD of the lung. The diagnosis of bronchiolitis obliterans is distinct from BOOP, an entity that is not associated with GVHD and is responsive to steroid therapy [18-21].

Previous reports [7,11,17] suggested that cGVHD is an important risk factor for the onset of BrOb in BMT patients and that this transplant complication is seen almost exclusively in recipients of allogeneic stem cells. Only 2 reports of BrOb in 3 autologous BMT patients have been published. Similarly, we have noted no BrOb in patients treated with autologous transplantation at the University of Minnesota. Clark et al. [8] reported that the incidence of BrOb 1 year after BMT was 1% in all allogeneic BMT patients and 4.6% in cGVHD patients. Holland et al. [9] reported that the incidence of BrOb in allogeneic BMT recipients was 2% and that it was 6% in cGVHD patients. Using stringent case ascertainment, we observed a 2%

Table 5. *Survival of Allogeneic BMT Recipients Diagnosed with BrOb*

Variable	No. of Patients		5-y Survival (95% CI)	*P* Value
	Total	Died		
Survival of recipients from the day of transplantation				
Among all allogeneic BMT recipients				
With BrOb diagnosed	48	26	10% (4%-29%)	<.01
No BrOb diagnosed	1741	1035	40% (38%-42%)	
Among recipients with GVHD				
With BrOb diagnosed	38	22	29% (16%-53%)	<.01
No BrOb diagnosed	494	242	54% (50%-59%)	
Survival of recipients diagnosed with BrOb from the onset of BrOb				
PFT status				
Responders and stable	15	4	67% (40%-94%)	.13
Nonresponders	13	7	46% (19%-73%)	
BrOb therapy				
ATG	6	4	NE	NS
Methylprednisolone	27	13	50% (30%-70%)	
Prednisone	14	8	43% (17%-69%)	
BrOb course				
Improved	23	4	79% (61%-97%)	<.01
Progressive disease	24	21	13% (0%-20%)	

CI indicates confidence interval; ATG, antithymocyte globulin; NS, not significant; NE, not evaluable.

1-year incidence of BrOb in allogeneic BMT recipients and a 6% incidence in patients already diagnosed with cGVHD (Figure 2). We recognize that our case review may be incomplete and may underestimate the actual BrOb incidence. The median time between BMT and diagnosis of BrOb was 465 days, and most patients developed BrOb >200 days after BMT, similar to earlier reports [13]. Long follow-up in our study identified a very late onset of BrOb in a few patients; 6 occurred beyond 3 years after BMT.

We noted that older donor and recipient age and prior acute GVHD were significant risk factors associated with BrOb. Clark et al. [7] reported that older age of recipients, male sex, cigarette-smoking history, lower FEV_1/forced vital capacity ratio before transplantation, HLA-nonidentical grafts, cGVHD, and immunosuppressive therapy with methotrexate were risk factors associated with airflow obstruction in recipients of bone marrow transplants. In that study, other factors—including underlying disease for BMT, conditioning regimen, and development of acute GVHD—were not associated with the airflow obstruction.

We observed that there was no association of BrOb development with the conditioning regimen or the way total body irradiation was delivered. In contrast to the Clark study, we found acute GVHD to be a significant risk factor and that sex, HLA mismatch, and immunosuppressive therapy were not risk factors for the development of BrOb. Underlying diseases were independently associated with BrOb onset in univariate analysis, but not in multivariate analysis. It is worth noting that previous studies did not associate the risk factors with the development of BrOb, but, rather, with airway obstruction measured by PFT.

We have detected that older age of sibling donors was associated with a higher incidence of BrOb. We are not aware of any previous analysis that includes the

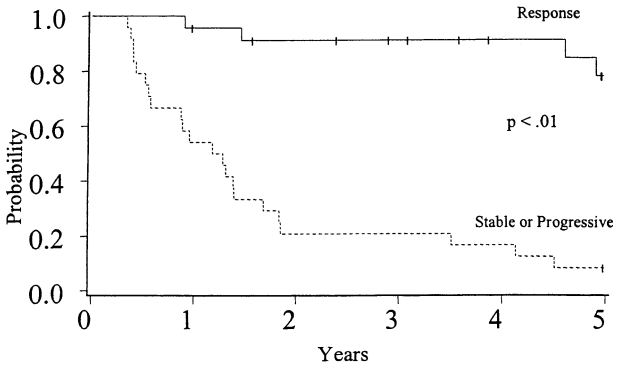

Figure 4. Survival of bronchiolitis obliterans patients with a clinical response after first-line treatment versus those with stable or progressive BrOb.

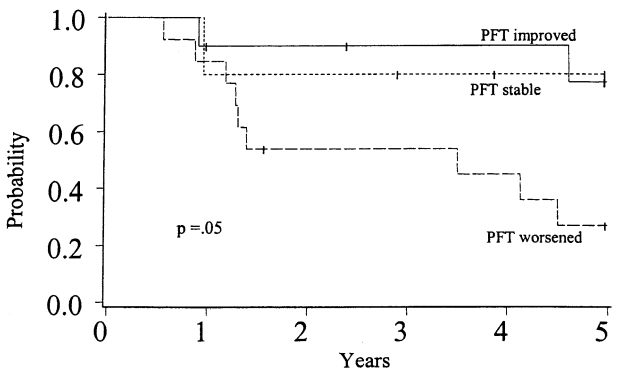

Figure 5. Survival of BrOb patients with improved versus stable or worsened PFT.

donor's age as a risk factor for BrOb after BMT. In the lung transplant literature, 1 study reported that donor age was not associated with BrOb [34], whereas another study found this association [35]. The reason why donor age might be a risk factor is open to speculation. It is possible that a younger immune system has enhanced immunologic plasticity, resulting in less BrOb and less GVHD. Although alloimmune reaction to the recipient's lung is the cause of BrOb development, the source of stem cells, related versus unrelated donor, HLA mismatch, and different types of GVHD prophylaxis were not identified as risk factors for BrOb.

In our studied population, 58 patients underwent cord blood transplantation, and none of them developed BrOb; however, most of these patients were children who had undergone transplantation recently, and it is too early to draw any conclusion about whether the incidence of BrOb in this group of patients will be different from the incidence in patients receiving transplants from other stem cell sources.

Holland et al. [9] reported that 6 of 7 patients diagnosed with BrOb died of pulmonary failure; 2 had *Pseudomonas* infection (1 also had CMV), and 1 had aspergillosis. The others had no evidence of infection, and BrOb caused the pulmonary failure. Paz et al. [11] found that 4 of 104 allogeneic BMT recipients developed BrOb. Two of these patients died of respiratory failure at days 300 and 360 after BMT. At the end of the second year after transplantation, the other 2 patients were still alive, but 1 required continuous ventilator support. Three of the 4 patients had opportunistic infections. In the study by Clark et al. [8], mortality was 65% in patients with obstructive lung disease at 3 years after transplantation, a significantly higher value than the 3-year mortality rate of 44% in a comparison group of 412 concurrent patients with cGVHD and normal pulmonary function. The median survival in that study was approximately 2 years after transplantation. In most of those patients, the causes of death were respiratory failure without infection. Although the median survival length and the chance of survival in patients diagnosed with BrOb are variable in different studies, development of BrOb has a major adverse effect on survival and is a frequent cause of death.

We analyzed the effects of different factors, such as serum immunoglobulin levels, response to therapy measured by improvement in PFT, type of BrOb treatment, and the clinical course of BrOb after treatment, on the 5-year survival. Improvement in the clinical course of BrOb after first-line therapy was significantly associated with a better 5-year survival of 79%, in contrast to only 13% if there was no response to initial therapy. In addition, we found notably poorer survival if BrOb occurred within the first 6 months after transplantation compared with later-onset BrOb. We have included immunoglobulin level in the survival analysis because hypogammaglobulinemia has been suggested as a factor associated with poor survival in transplant patients, and intravenous immunoglobulin replacement has been proposed as another supportive measure in BrOb treatment. In a controlled trial of long-term administration of intravenous immunoglobulin [36], it was shown that this therapy was associated with lower risk of BrOb. We observed a trend that older BrOb patients had a higher likelihood of having low immunoglobulin levels, but there was no significant difference in 5-year survival between patients with BrOb who had low or normal serum immunoglobulin G at the time of BrOb diagnosis.

There is no standardized approach for the treatment of BrOb in post-BMT transplant patients. In study by Sanchez et al. [37], long-term allogeneic bone marrow transplantation survivors affected by obstructive airway disease were analyzed for a pulmonary response to prednisone, cyclosporine, or azathioprine. No differences in response between immunosuppression modalities were detected; however, it was noted that the optimal response occurred in the first 6 months of treatment and that prolonged immunosuppression may not be warranted. It is plausible that our study, which required a sustained response to therapy, underestimated the treatment response rate, because treatment failure resulted in more frequent visits to transplant centers and because patients with stable or improved disease were usually followed up by local physicians. Patients with BrOb in our institution were treated with intravenous weekly methylprednisolone, alternate-day prednisone and cyclosporine, or antithymocyte globulin; boluses of methylprednisolone, prednisone, and cyclosporine or azathioprine; or prednisone alone. We observed no significant difference in the 5-year survival of patients treated with these 3 different therapies. Lymphocytic bronchiolitis, probably an earlier and possibly reversible form of BrOb [38], was detected in 2 patients in our study. It is interesting to note that both patients improved clinically after initial therapy. A number of other therapies have been suggested, such as extracorporeal photophoresis, hydroxychloroquine, mycophenylate, and rapamycin. In our study, 5 patients were treated with thalidomide, with similar outcomes; 1 patient responded, 3 had stable disease, and 1 had progressive disease. We found that thalidomide had no effect on improving survival in patients with cGVHD [39] and observed only this limited activity in patients with BrOb.

Unfortunately, no model of post-BMT BrOb exists. Airway injury is predominantly immunologic in BrOb after lung transplantation [40], with increased levels of T-helper type 1 cytokines (interferon γ and interleukin-2) and CXC chemokines (regulated on

activation, normal T cells expressed and secreted; monocytic chemotactic protein-1; and interleukin-8) [41-45]. It is hypothesized that in cGVHD, endothelial cell injury mediated by cytotoxic T lymphocytes may underlie processes leading to tissue fibrosis [46,47]. More selective immune suppression, modulation of chemokine responses [48,49] and protection of pulmonary endothelium may become a goal of future therapies to prevent and treat BrOb.

Patients with BrOb and cGVHD who are younger or have younger donors and a BrOb diagnosis earlier than 6 months after transplantation have a high likelihood of poor response to first-line therapy. These patients should be offered novel treatment strategies in future studies.

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